IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NOVARTIS PHARMACEUTICALS CORPORATION and ASTEX THERAPEUTICS LTD. Plaintiffs, v. MSN PHARMACEUTICALS INC. and MSN LABORATORIES PVT. LTD., Defendants.	C.A. No. 21-870-GBW (CONSOLIDATED) [redacted] **REDACTED VERSION**

MSN'S CONTINUED POST-TRIAL FINDINGS OF FACT

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83. MSN's Notice Letter disclosed that a POSA would have chosen Compound 338 as a lead compound from Brain and could have obtained "more exact IC50 values… without an undue burden." D.I. 114 at (pdf) 718, 740, 760, 764, 776, 780. Accordingly, MSN has consistently contended that the '355 and '630 patents are obvious over Compound 338, which is admitted prior art. *Id.* at (pdf) 696-97. Dr. Micalizio's report analyzed obviousness to the extent that Compound 338 and other compounds in Brain are admitted prior art, but did not opine on what disclosure in the '355 and '630 patents was prior art. *Id.* at (pdf) 690.

84. It is undisputed that there can be more than one lead compound in the prior art. Tr. 475:20-24 (Toogood). Further, it is undisputed that "there's no reason to include or exclude any of [Brain] compounds from consideration" if a POSA was looking to provide selectivity against other CDKs. Tr. 506:24-507:5 (Toogood).

85. MSN's expert, Dr. Micalizio, testified that he considered palbociclib as one lead compound, but also that palbociclib would guide a POSA to consider Compound 338 as a lead compound also. Tr. 196:11-22, 95:2-100:18 (Micalizio).

86. Plaintiffs never rebutted MSN's expert, Dr. Micalizio, that a POSA would have expected Compound 338 to interact with the four key regions in the same way as the compounds disclosed in the Pfizer SAR Papers, but instead only presented hypothetical modifications that could have been made to a compound's core or side groups. *See* D.I. 138, 18 (citing Tr.408:4-410:25, Pls. FOF, ¶32); Tr. 104:16-107:13 (Micalizio).

87. After the publication of Toogood 2001, Toogood 2005 concluded that a cyclopentyl at N8 "provided the best combination of potency and selectivity" for CDK4. JTX0094-0003 at ¶4; Tr. 82:8-23 (Micalizio). It is undisputed that a later Pfizer SAR Paper may restate or revise the perspective of an earlier paper from evolving data and new information. Tr. 472:12-15 (Toogood).

88. Toogood 2005 informed a POSA that selectivity can be achieved by installing the "magic N" without a C5 methyl. Tr. 83:8-84:9 (Micalizio).

89. It is undisputed that the term "magic N" stems from Toogood 2005's observation that the N pyridyl group conferred a high level of selectivity. Tr. 499:24-500:4 (Toogood).

90. A singular modification to "a prior art compound [338] that a POSA would know and a… molecular change in that… compound that was taught in the prior art" results in ribociclib. Tr. 674:10-24 (Micalizio).

91. Plaintiffs and their experts failed to attribute unasserted patents listed in the Orange Book and the hormone therapies that must be co-administered with ribociclib in their secondary consideration analyses. Tr. 666:13-668:16 (Vellturo); 544:3-16 (Cohen); 698:12-19 (Stebel); DTX319.

92. A POSA would have expected a more selective CDK4 inhibitor would have arrest of cell cycle at G1 phase. Tr. 510:12-512:1 (Toogood); JTX149_0013; 674:1-676:8.

93. Any benefit to treatment with CDK4/6 inhibitors is shared by all drugs in that class. Tr. 698:3-11 (Stebel). A POSA would have expected a drug in phase III clinical trial to meet its clinical endpoints. 699:19-700:3; 604:21-605:4 (Cohen). POSAs would have been surprised that palbociclib did not have statistically significant OS improvement. Tr. 742:11-20 (Stebel).

94. The OS improvement shown in palbociclib trials is clinically meaningful, similar to OS improvements from the ribociclib trials. Tr. 605:8-23, 563:2-15, 564:25-565:10 (Cohen); 711:5-11 (Stebel).

95. Plaintiffs and their expert, Dr. Cohen, omitted the OS improvement shown in abemaciclib trials, which are similar to ribociclib. Tr. 587:5-9 (Cohen); Tr. 710:4-711:4 (Stebel)

(discussing DDX312). Moreover, abemaciclib includes more approved indications, such as treatment as a monotherapy. Tr. 693:15-694:15 (Stebel) (discussing DDX309).

96. Ribociclib has not been shown to be superior to the other CDK4/6 inhibitors because there are no head-to-head studies, abemaciclib is approved for more indications, abemaciclib has a less severe side effect profile, and abemaciclib and palbociclib can be used with tamoxifen. Tr. 590:13-16, 591:14-20, 592:3-6, 607:22-608:8, 608:15-610:18 (Cohen); 693:12-696:6, 697:24-698:2, 707:1-708:20, 708:24-709:2 (Stebel); JTX0116_0080.

97. Kisqali® from 2017 through 2023 has the smallest market share of CDK4/6 inhibitors, but a disproportionately outsized share of voice in marketing. Tr. 765:9-766:13, 767:16-768:19, 771:21-773:7 (Hofmann); PTX341; PTX342; JTX400; JTX124; [redacted].

98. [redacted]. Tr. 769:21-771:6 (Hofmann); [redacted]

99. It is undisputed that prospective marketplace metrics are mere "indicator[s]" where market shares are going, including NBRX. Tr. 643:19-645:5 (Vellturo); 814:22-815:5, 815:20-816:10 (Hofmann). Moreover, even the retrospective NBRX figures refer to only new prescriptions, a small subset of the total market. Tr. 766:14-767:1 (Hofmann).

100. From pleadings through the Pre-Trial Order Plaintiffs maintained two specific theories of a long-felt but unmet need. *Supra.* at ¶53. Plaintiffs move the goal-post yet again in their Post-Trial Brief. *Cf. id. with* D.I. 138 at 30-31. At trial, Plaintiffs also introduced new evidence for industry praise, never before relied upon. Tr. 597:15-598:25 (Cohen); 727:25-728:11 (Stebel).

101. Use of Kisqali in pre- or perimenopausal women would be a detriment to quality of life, because they are thrust into menopause, which does not occur with other CDK4/6 inhibitors. Tr. 712:13-713:18 (Stebel).

102. The only admissible evidence Plaintiffs introduce to support industry praise is the NCCN Guidelines, which are "not in the business of praising any product." Tr. 613:21-614:11 (Cohen); 707:9-708:20 (Stebel). The NATALEE trial outcome has not resulted in an eBC indication for Kisqali—the same indication Verzenio already possesses. JTX268; Tr. 617:22-618:5 (Cohen).

103. Plaintiffs and their expert Dr. Toogood have no knowledge of why other companies discontinued their CDK discovery programs. Tr. 474:14-475:8 (Toogood).

104. Plaintiffs and their expert Dr. Toogood have no knowledge of why generic companies chose not to litigate the validity of the Asserted Patents. *Id.* at 513:14-514:13.

105. Plaintiffs' expert, Dr. Toogood, testified that "the art is unpredictable," thus, differentiating the useful compounds recited in claim 1 from the useless compounds would require an iterative series of experiments for the nearly infinite compounds encompassed. Tr. 414:19-21 (Toogood); Tr. 133:1-12 (Micalizio) (discussing the quantity of experimentation).

106. The examples in the '225 patent's specification do not offer sufficient guidance on how to make useful compounds outside the limited chemical space the compound encompass. Tr. 127:3-130:25 (Micalizio).

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CERTIFICATE OF SERVICE

I, Karen L. Pascale, Esquire, hereby certify that on April 19, 2024, I caused to be electronically filed a true and correct copy of the foregoing sealed document with the Clerk of the Court using CM/ECF, and in addition caused true and correct copies of the foregoing sealed document to be served upon the following counsel of record by electronic mail::

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